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<p>(21) International Application Number: PCT/EP98/03946 (22) International Filing Date: 24 June 1998 (24.06.98) (30) Priority Data: MI97A001523 27 June 1997 (27.06.97) IT (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).</p>		<p>(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: ACE-INHIBITOR NITRIC SALTS</p> <p>(57) Abstract</p> <p>Ace-inhibitor nitric salts having formulae (I), (II), (III).</p> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> <p>(I)</p> </div> <div style="text-align: center;"> <p>(II)</p> </div> <div style="text-align: center;"> <p>(III)</p> </div> </div>		

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ACE-INHIBITOR NITRIC SALTS

The present invention relates to products having an antihypertensive activity combined with a platelet-antiaggregating activity, and pharmaceutical compositions thereof.

In particular, it relates to products having an improved antihypertensive activity and fewer side effects, in particular in the bronchi, compared to the products currently being marketed as antihypertensive agents. The antihypertensive activity is combined with a platelet-antiaggregating activity.

Antihypertensive agents are known in the art. Particularly known are ACE inhibitors, which represent a first-choice pharmacological measure in the treatment of cardiovascular diseases such as hypertension, angina, myocardial ischaemia, congestive heart failure, and others. ACE inhibitors act on the renin-angiotensin system which releases angiotensin II, one of the most effective hypertensive agents known. More precisely, these drugs inhibit the activity of the angiotensin converting enzyme, a carboxypeptidase which is mostly present in lungs, kidneys, and vessels. The action of this enzyme is not specific. It inactivates plasma bradykinin,

which possesses a vasodilatory activity. and also helps diuresis and, in particular, natriuresis. In other terms, plasma bradykinin possesses opposite effects compared to those of angiotensin II. Therefore, ACE inhibitors prevent formation of angiotensin II and, at the same time, degradation of bradykinin. Hence, ACE inhibitors certainly represent one of the most significant pharmacological innovation of the past few decades.

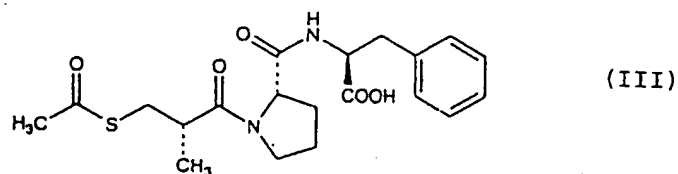
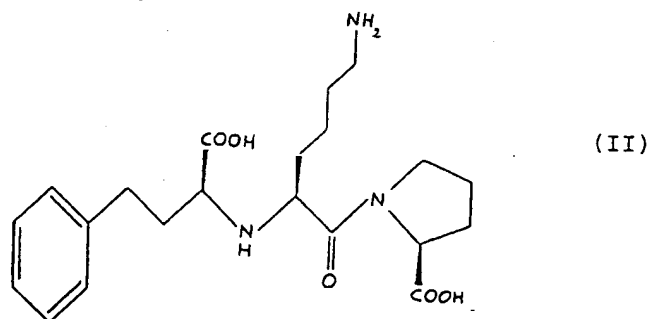
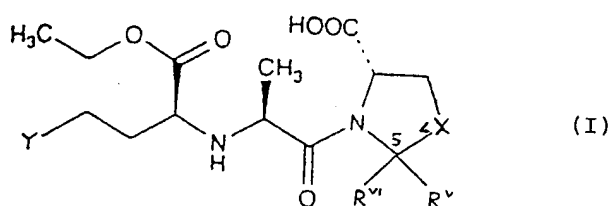
However, the administration of ACE inhibitors is often (about 20 to 30% of the cases) accompanied by side effects in the respiratory system, such as cough, dyspnea, bronchoconstriction. Furthermore, these drugs show a rather limited therapeutic profile, for example they have no platelet-antiaggregating activity, so that, in the above cardiovascular treatments, they are often associated with other drugs having an antiaggregating activity. For example, in the treatment of myocardial infarction and prevention of relapses, it is essential to use a multiple cardiovascular therapy including, among others, the association of an antihypertensive with an antiaggregating agent.

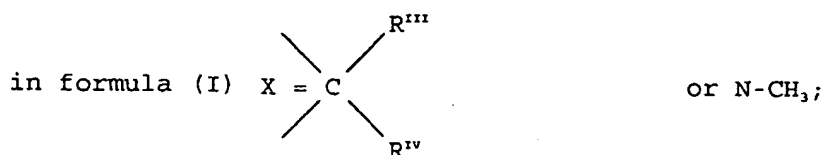
It was felt the need for drugs with a better therapeutic profile and fewer side effects, in particular, at the respiratory system, for example the bronchi.

The Applicant has unexpectedly and surprisingly found a

specific class of ACE-inhibitor salts characterised by the fact that they possess, compared to other salts of the same compounds, a better antihypertensive activity and have fewer side effects in the bronchi.

An object of the present invention is, therefore, the nitric salts of ACE inhibitors having the following formulas:

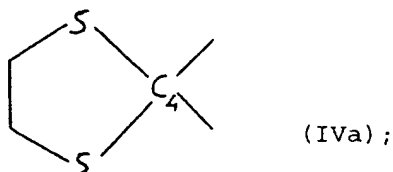




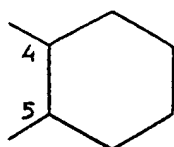
Y = CH₃, phenyl;

R^{III} = H,

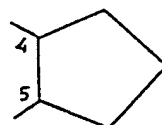
R^{III} together with R^{IV} forms the following ring in the carbon at position 4



R^{III} together with R^V (carbons at positions 4 and 5) forms the cyclohexane or cyclopentane rings



(IIIa)



(IIIb);

R^{IV} = H, or R^{IV} forms with R^{III} ring (IVa);

R^V = H, or a free valence, or R^V forms with R^{III} rings (IIIa) or (IIIb);

R^{VI} = H, or a single bond -O when R^V is a free valence so as to form a ketone group with the carbon atom at position 5.

The preferred nitrate salts of formula (I) include:

when X = C (R^{III}) (R^{IV}) as above defined, Y = phenyl, R^{III} = R^{IV}

= $R^V = R^{VI} = H$, the residue of Enalapril;
as in Enalapril but with R^{III} which, together with R^{IV} , forms ring (IVa), the residue of Spirapril;
as in Enalapril but with R^{III} which, together with R^V , forms ring (IIIb), the residue of Ramipril;
as in Enalapril but with $Y = CH_3$ and R^{III} which, together with R^V , forms ring (IIIa), the residue of Perindopril;
as in Enalapril, but with $X = N-CH_3$, R^V is a free valence and $R^{VI} = -O$ so as to form with carbon atom C_5 a ketone group, the residue of Imidapril.

The compounds of the classes of the invention, which are the precursors of the salts, are used as optically-active single isomers or as mixtures thereof or in the form of racemates.

The precursor of class II is known as Lisinopril, that of class III is known as Alacepril. The precursors are prepared according to the methods described in "The Merck Index, Ed. 12", herein incorporated by reference.

The salts of the present invention are prepared according to the following method. The substance to be salified is dissolved in an organic solvent, not containing in the molecule free hydroxyl groups, and then a stoichiometric amount of concentrated nitric acid is added. The salt is recovered by filtration and washed several times with a

solvent, for example that used in the reaction. Polar organic solvents are preferred, such as , for example, acetonitrile, ethyl acetate, and others.

It has surprisingly been found that the compounds of the present invention improve, compared to the same substances and ACE salts generally, the pharmacological profile of the above ACE inhibitors and, additionally, exhibit a more favourable general and regional tolerability.

The compounds of the present invention can be used as cardiovascular drugs, in particular in the treatment of hypertension, angina, myocardial ischaemia, congestive heart failure.

The salts of the present invention are formulated in the corresponding pharmaceutical compositions according to the methods well known to those skilled in the art, which are, for example, described in Remington's Pharmaceutical Sciences, Ed. 15.

The examples below are meant to describe the invention and should not be understood as a limitation of same.

EXAMPLE 1

Synthesis of (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (Enalapril), and obtainement of the nitrate salt in acetonitrile

A mixture of ethyl-2-oxo-4-phenylbutyrate (2.1 g) and

L-alanyl-L-proline (0.4 g) in ethanol/water 1/1 was treated slowly at room temperature with a solution of sodium cyanoborohydride (0.4 g) in ethanol/water 1/1.

At the end of the reaction, the product was absorbed on a strong acid ion exchange resin and eluted with an aqueous solution containing 2% (v/v) of pyridine. The fractions which contained the product were lyophilised to obtain the crude compound. Chromatography then allowed isolation of the desired isomer (-) practically pure (0.24 g).

The isomer was then dissolved in acetonitrile and treated, maintaining the reactor in an ice bath, with a stoichiometric amount of concentrated nitric acid dissolved in acetonitrile. After cooling and filtration, the solid was washed with cold acetonitrile and a 97%-pure (HPLC: high pressure liquid chromatography) Enalapril nitric salt was recovered. A 99%-pure (HPLC) salt could be obtained by crystallisation from acetonitrile.

EXAMPLE 2

Synthesis of Enalapril, and obtainement of the nitrate salt in ethyl acetate

A mixture of ethyl-2-oxo-4-phenylbutyrate (15 g), L-alanyl-L-proline (9 g), molecular sieves 3A° (40 g) and Raney nickel (10.8 g) in ethanol (300 ml) was hydrogenated at room temperature and at a pressure of about 3 atm. up to the

hydrogen is not consumed any more. After filtration of the undissolved substance (washing well with ethanol, the solvent was evaporated under vacuum to obtain a mixture of diastereoisomers formed of 85% by the expected product (by HPLC). The obtained product was dissolved in a mixture made up of 200 ml of water and 70 ml of methyl acetate. By keeping the solution under stirring, the pH was adjusted to 8.6 with 50% NaOH. The organic phase was separated and the aqueous phase was thoroughly washed with ethyl acetate (3 x 50 ml). The aqueous phase was adjusted to pH 4.3 with hydrochloric acid, saturated with sodium chloride and then extracted with ethyl acetate (4 x 100 ml). After drying with sodium sulphate and evaporating the solvent off under vacuum, the residue was dissolved in ethyl acetate maintaining the reactor in an ice bath, and salified by treating with a stoichiometric amount of concentrated nitric acid. After stirring for two hours, it was cooled, filtered, washed with ethyl acetate and recrystallised from acetonitrile to obtain 12.5 g of nitric salt of the isomer (-), about 99%-pure (by HPLC).

EXAMPLE 3

Acute toxicity

A group of 10 mice (weight 15 to 25 g) received a single oral dose of 100 mg/Kg. All the animals survived during the observation period (14 days). No toxicity symptom was

observed.

EXAMPLE 4

Antihypertensive activity

The antihypertensive activity of the nitrate salts of the compounds of the invention was determined in accordance with the method of Laubie et al., J. Cardiovasc. Pharmacol. 6, 1076, 1984. N° 6 rats weighing about 200 to 250 g were used per experimental group. Four groups were formed, which were intraperitoneally treated respectively as shown below:

- Enalapril maleate 100 µg/Kg
- Enalapril maleate 300 µg/Kg
- Enalapril nitrate 100 µg/kg
- Enalapril nitrate 300 µg/kg

The doses are referred to the amount of Enalapril (cation) in the salt. The antihypertensive response was evaluated as per-cent inhibition of the hypertension induced by the administration of a dose of 100 µg/Kg i.v. of angiotensin I as described in the above article.

The results are shown in Table I

TABLE I

COMPOUND	DOSE (µg/Kg/i.p.)	Inhibition % for angiotensin-I- induced hypertension
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Enalapril maleate	100	18
Enalapril maleate	300	55
Enalapril nitrate	100	35
Enalapril nitrate	300	67

EXAMPLE 5

Pharmacological effects of the salts of the invention on bronchial spasm induced by administration of substance P

Activity was evaluated measuring the strengthening of bronchial spasm induced by substance P, determined in accordance with the method of Subissi et al., Br. J. Pharmacol. 100, 502-6, 1990. The model described by Subissi is predictive of bronchial side effects due to the administration of ACE inhibitors.

Four groups (6 animals/group) of female Guinea pigs weighing about 300 to 400 g were anaesthetised with ethyl urethane (200 mg/Kg) under artificial pressure at constant positive pressure. The compounds were administered intraperitoneally 30 minutes before substance P. The salt doses administered were the same as in Example 4. The changes in tidal air were then measured in accordance with the method of Konzett, Arch. Exp. Pathol. Pharmacol. 195, 71, 1940, before and after the administration of substance P (200 µg/Kg), with or without the test salts, i.e. Enalapril maleate and nitrate.

The results are shown in Table II

As seen from the data, Enalapril nitrate possessed a better respiratory profile than Enalapril maleate at both tested doses.

TABLE II

COMPOUND	DOSE (μ g/Kg/i.p.)	Tidal air change % in bronchial spasm induced by substance P
Enalapril maleate	100	+ 16
Enalapril maleate	300	+ 28
Enalapril nitrate	100	- 5
Enalapril nitrate	300	- 7

EXAMPLE 6

Platelet-antiaggregating activity

The in-vivo model described by Pinon et al., J. Pharm. Methods 12, 79-84, 1984, was used.

Two groups of 6 rats each, weighing about 200 to 250 g, were treated with an oral dose of 10 mg/Kg/die of Enalapril maleate or nitrate respectively (the dose is referred to the amount of Enalapril cation in the salt) for five days, while a third group acted as a control group. About 18 hours before the last treatment, the animals were fasted. One hour after

this treatment the animals were anaesthetised with 10% ethyl urethane (1 g/Kg intraperitoneally) and the left jugular vein and the right carotid artery were cannulated. Collagen (type 6, Sigma) was then administered intravenously at a dose of 2 mg/Kg. Three minutes later two blood samples, A and B, were collected from the carotid artery of each animal.

1.6 ml of EDTA/formalin buffer (24 mM tetrasodium EDTA, 1.3 mM KH_2PO_4 , 13.4 mM Na_2HPO_4) was added to the first sample (sample A) containing 0.4 ml of blood.

The second blood sample (sample B) had the same volume as the previous sample (0.4 ml of blood) but, instead of the buffer, 1.6 ml of a saline solution (physiological NaCl solution) was added.

The samples were then transferred into 5-ml test tubes and allowed to stand at room temperature for 15 minutes.

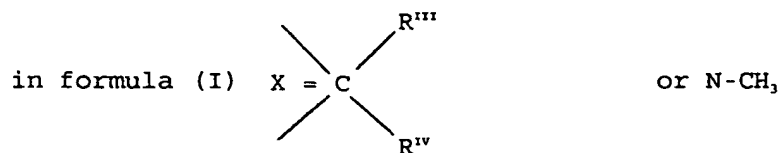
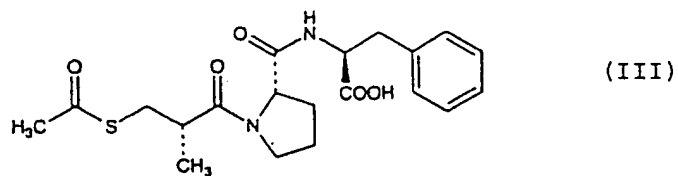
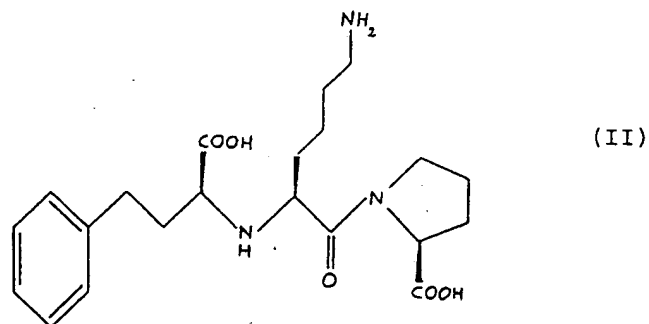
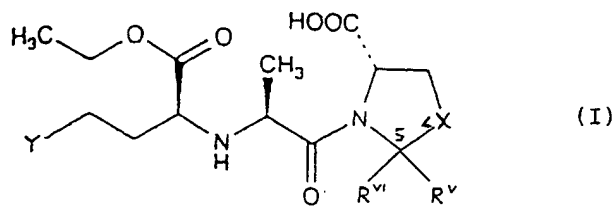
A microscope platelet count was then performed. The platelet count in samples B and A represent the total number of platelets and the total number of aggregated platelets respectively. The results shown in Table III are expressed as a % of platelet aggregation and are referred to the % value obtained in the control group.

TABLE III

COMPOUND	DOSE/die (mg/Kg/os)	Antiaggregating activity %
Enalapril maleate	10	5
Enalapril nitrate	10	58

CLAIMS

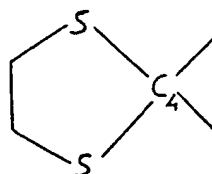
1. Nitric salts of ACE inhibitors having the following formulas:



$Y = CH_3$, phenyl;

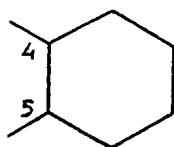
$R^{III} = H$,

R^{III} together with R^{IV} forms the following ring in the carbon at position 4

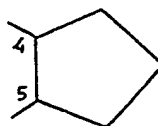


(IVa);

R^{III} together with R^V (carbons at positions 4 and 5) forms the cyclohexane or cyclopentane rings



(IIIa)



(IIIb);

$R^{IV} = H$, or R^{IV} forms with R^{III} ring (IVa);

$R^V = H$, or a free valence or R^V forms with R^{III} rings (IIIa) or (IIIb);

$R^{VI} = H$, or a single bond -O when R^V is a free valence so as to form a ketone group with the carbon atom at position 5.

2. Nitric salts according to claim 1, wherein, in formula (I), $X = C(R^{III})(R^{IV})$, $Y = \text{phenyl}$, $R^{III} = R^{IV} = R^V = R^{VI} = H$, the residue of Enalapril;
as in Enalapril but with R^{III} which, together with R^{IV} ,

forms ring (IVa), the residue of Spirapril;
as in Enalapril but with R^{III} which, together with R^V ,
forms ring (IIIb), the residue of Ramipril;
as in Enalapril but with $Y = CH_3$ and R^{III} which, together
with R^V , forms ring (IIIa), the residue of Perindopril;
as in Enalapril, but with $X = N-CH_3$, R^V is a free valence
and $R^{VI} = -O$ so as to form with carbon atom C_5 a ketone
group, the residue of Imidapril.

3. Nitric salts according to claim 2, wherein, in formula (I), $X = C(R^{III})(R^{IV})$, $Y = \text{phenyl}$, $R^{III} = R^{IV} = R^V = R^{VI} = H$, the residue of Enalapril.
4. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as anti-hypertensive agents.
5. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as antiaggregating agents.
6. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as anti-hypertensive and antiaggregating agents.
7. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as cardiovascular agents for the treatment of hypertension, angina, myocardial ischaemia, congestive heart failure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03946

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D207/16 C07K5/068 A61K31/40 A61K38/05		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D C07K A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5 645 839 A (CHOBANIAN ARAM ET AL) 8 July 1997 see the whole document ---	1-7
A	CHEMICAL ABSTRACTS, vol. 115, no. 15, 14 October 1991 Columbus, Ohio, US; abstract no. 149997, XP002085266 see abstract & R.J. KATZ ET AL.: CIRCULATION, vol. 83, no. 4, 1991, pages 1271-1277, --- -/--	1-7
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Date of the actual completion of the international search	Date of mailing of the international search report	
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03946

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 116, no. 19, 11 May 1992 Columbus, Ohio, US; abstract no. 187771, XP002085267 see abstract & ALI F. HAJJ-ALI ET AL.: EUR. J. PHARMACOL., vol. 212, no. 2-3, 1992, pages 279-281, ---	1-7
A	CHEMICAL ABSTRACTS, vol. 119, no. 5, 2 August 1993 Columbus, Ohio, US; abstract no. 40531, XP002085268 see abstract & F.J. HOCK ET AL.: BIOL. NITRIC OXIDE, PROC. INT. MEET., 2ND, vol. 1, 1991, pages 279-281, ---	1-7
A	CHEMICAL ABSTRACTS, vol. 124, no. 13, 25 March 1996 Columbus, Ohio, US; abstract no. 164763, XP002085269 see abstract & G.J. DUSTING ET AL.: AM. J. CARDIOL., vol. 76, no. 15, 1995, pages 24e-7e, ---	1-7
A	CHEMICAL ABSTRACTS, vol. 125, no. 11, 9 September 1996 Columbus, Ohio, US; abstract no. 132132, XP002085270 see abstract & J.R. RUMBLE ET AL.: J. HYPERTENS., vol. 14, no. 5, 1996, pages 601-607, ---	1-7
A,P	CHEMICAL ABSTRACTS, vol. 128, no. 4, 26 January 1998 Columbus, Ohio, US; abstract no. 30226, XP002085271 see abstract & H. WATANABE ET AL.: AM. HEART J., vol. 134, no. 4, 1997, pages 614-621, ---	1-7
A,P	CHEMICAL ABSTRACTS, vol. 128, no. 21, 25 May 1998 Columbus, Ohio, US; abstract no. 253007, XP002085272 see abstract & CN 1 141 771 A (JIA LI, PEOP. REP. CHINA) -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/03946

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5645839 A	08-07-1997	NONE	



Alma Rubio
30.01.2006 10:06

To: Nathalie Jenni/Actelion@Actelion
cc:
Subject: RE: FW: FW: QLAB / Actelion MSA

Dear Nathalie

I hope you had a nice weekend!

Please find below the feedback from EMSI. Let me know what you think.

Many thanks,

Alma

Alma Rubio PhD
Clinical Research Scientist / Global Medical Marketing
Actelion Pharmaceuticals Ltd / Gewerbestrasse 16 - CH-4123 Allschwil / Switzerland/
Direct: Tel: +41 61 565 5306 / Fax: + 41 61 565 5484 / alma.rubio@actelion.com / www.actelion.com
----- Forwarded by Alma Rubio/Actelion on 30.01.2006 10:04 -----



Doug Wilson
<dwilson@emsinet.co
m>

27.01.2006 22:54

To: "Alma.Rubio@actelion.com" <Alma.Rubio@actelion.com>
cc:
Subject: RE: FW: FW: QLAB / Actelion MSA

Dear Alma,

We found responses for items 5, 7, 11 and 12 as you indicated and our attorney has approved items 7 as long as Actelion agrees that mileage will be reimbursed without need for receipts since it would be impossible to provide those. He has also approved item 11 (Section 5.2 as written).

The outstanding issues are items 5 and 12 and we would propose the following options:

Item 5: We requested a retainer or deposit since services are being provided in the U.S. and Actelion is a Swiss company. We understand that this is against Actelion company policy so we would propose the option of 15-day payment terms in lieu of a deposit.

Item 12: We requested a mutual 30-day termination for convenience and the contract only provides for termination for cause. As an alternative, we would propose a longer notice period of 90 or 120 days. If no termination for convenience is allowed in a Master Services Agreement, we would need the ability to not accept future projects if we are concerned that we could not fulfill the requirements.

Also, we had agreed to Actelion rejecting our proposed change numbered 13; but we would need the following sentence to be added to the end of the first paragraph in Section 3.2: "The obligations stated in this paragraph shall survive any termination of this Agreement."

I have attached the most recent version of the agreement along with the revised proposal and confidentiality policies as you requested. The remaining items are business related and should your legal department not agree to these changes, I am authorized to negotiate on EMSI's behalf. I

am
available for a call any day next week but Wednesday.

I look forward to finalizing these documents.

Kind regards,

Doug

Doug Wilson
Vice President of Sales, Health Services
(214) 689-3630
dwilson@emsinet.com

-----Original Message-----

From: Alma.Rubio@actelion.com [mailto:Alma.Rubio@actelion.com]
Sent: Thursday, January 26, 2006 8:35 AM
To: Doug Wilson
Subject: RE: FW: FW: QLAB / Actelion MSA

Hi Doug

We have already responded to items 5, 7, 11 and 12. Could your attorney please clarify the issues? We could also have a teleconference to discuss those issues.

I would also like to finalize this agreement asap so we could start working on the project. We expect the first patient to be included in the study by the end of February.

Thank you very much for your feedback.

Best regards, Alma

Doug Wilson

<dwilson@emsinet. To:
"Alma.Rubio@actelion.com'" <Alma.Rubio@actelion.com>
com> cc:

Subject: RE: FW: FW: QLAB /

Actelion MSA

25.01.2006 19:19

Hi Alma,

I apologize for the delay in responding to you. Our attorney has reviewed the responses from your legal department and has indicated that Actelion has